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A general method for the direct transformation of common tertiary amides into ketones and amines by addition of Grignard reagents

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ABSTRACT

The direct transformation of amides into ketones by addition of organometallic reagents has attracted the attention of organic chemists for a long time. However limited methods are reliable for common amides and have found synthetic applications. Here we report a method featuring *in situ* activation of tertiary amides with triflic anhydride (Tf_2O) followed by addition of Grignard reagents. The method displays a good generality in scope for both amides and Grignard reagents, and it can be viewed as the acylation of Grignard reagents using amides as stable and selective acylating agents. Moreover, this deaminative alkylation reaction provides a mild method for the *N*-Deacylation of amides to give free amines.

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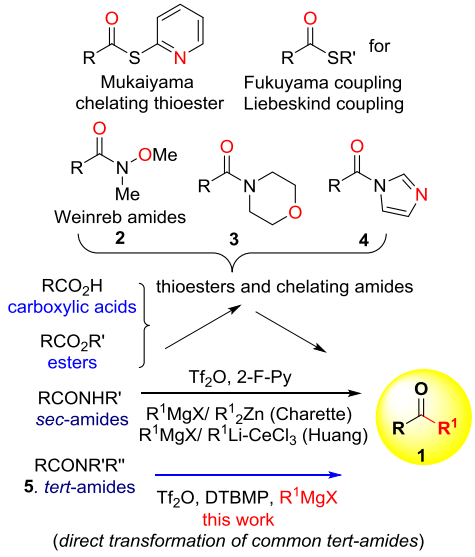
1. Introduction

Due to their multiple reactivities, ketones (**1**) are perhaps the most versatile class of molecules for C–C bond formation in organic chemistry. The rich chemistry of ketones ranges from enol/enolate-based reactions to electrophilic carbonyl-based reactions. In addition, ketones are found in many bioactive natural products[1] and medicinal agents.[2] Consequently, although numerous methods have been established, the synthesis of ketones still attracts current attention.[3] Among the methods for ketone synthesis, those based on the addition of organometallic reagents to carboxylic acid derivatives are the most popular.[4] However, due to the low reactivity of the carboxylic acid derivatives (except for acid chlorides) compared to ketones, over addition that leads to tertiary alcohols is difficult to be avoided.[5] To tackle this problem, specially designed chelating amides (e.g., **2**,[6] **3**,[7] **4**[8]) and thioesters[9] have been developed as vehicles for the indirect transformation of carboxylic acids and esters into ketones (**1**) (Scheme 1). Among the chelating amides developed so far, the most well-known and reliable one is the *N*-methyl-*N*-methoxyamides **2**, known as Weinreb amides.[6] Recently, by using amide activation strategy, Charette[10a] and our research group[10b,c] have developed independently the direct transformations of secondary amides into ketones by addition of Grignard/organozinc reagents, and organocerium reagents, respectively. However, the development of reliable methods for the direct transformation of common tertiary amides into ketones remains a formidable challenge.



Scheme 1. Representative general methods for the transformation of carboxylic acid derivatives into ketones.

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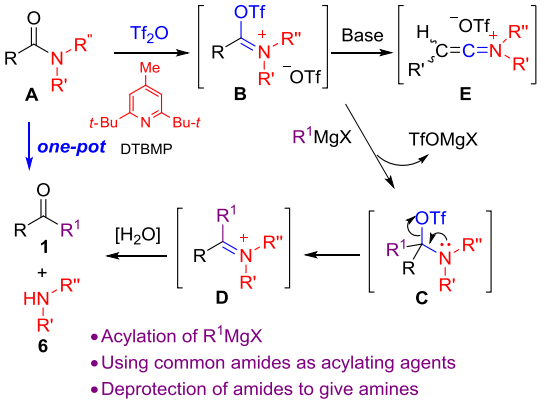
Unactivated[11] common tertiary amides are a class of highly stable and easily available carboxylic acid derivatives.[12] These features make them very useful starting materials and intermediates in organic synthesis.[13] Thus, the deacylation of amides to give amines under mild conditions is an important transformation in the synthesis of alkaloids and *N*-containing pharmaceutics.[13] In addition, tertiary amido groups also serve as powerful directing groups in directed lithiation[14] and C–H functionalization reactions.[15] In this context, after C–H functionalization, the transformation of the directing amido groups into other functional groups such as ketones is imperative.[8c,14b,d,l]

However, due to the higher stability of amides compared to esters, the direct transformation of common tertiary amides **5** into ketones by addition of organometallic reagents is more challenging.[16] As a result, although much efforts have been devoted,[7c,17–22] very few examples are reliable for common amides[23] and have found synthetic applications.[24] For example, while the methods based on the addition of RLi are reliable for chelating alkoxy/amino amides[18] and benzamides,[17c] low yields were obtained from aliphatic amides.[17c,f] In addition, for sterically hindered *N*,*N*-diethyl and *N*,*N*-diisopropyl aromatic amides, the most useful directing groups for the directed lithiation,[14] those methods are not efficient due to the competing metalation.[14b,24c,25] Other methods are either restricted to *N*,*N*-dimethylamides and cyclic amine-based amides[21] or limited to the synthesis of methyl ketones.[22] Strangely, Collins' high-yielding method,[20] featuring the use of both alkyl and aryl lanthanum triflates, has only one unsuccessful application[24c] since its publication in 1987. Moreover, while the addition of Grignard reagents to *N*,*N*-dimethylamides has been reported,[17f] no synthetic application can be found, and the reactions failed with *N*,*N*-diethylamides.[14d] Thus, reliable and general methods for the direct transformation of common tertiary amides into ketones by addition of Grignard reagents[26] are highly demanding. As a continuation of our efforts in developing C–C bond-forming methods from amides,[10b,c,27] we report herein a versatile and direct synthesis of ketones from common tertiary amides by addition of Grignard reagents. The application of this deaminative alkylation reaction for the deacylation of amides to give free amines is also demonstrated.

2. Results and discussion

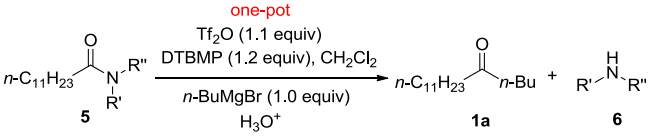
Our approach is based on the tactic of *in situ* activation of "inert" amide to form a highly reactive intermediate. In this context, triflic anhydride (Tf_2O)[28] has been shown to be an advantageous activating reagent allowing the Vilsmeier-Haack-Arnold-type formylation[29a] and isobutanoylation[29b] of soft or stabilized nucleophiles.[29c–f] Our previous work has demonstrated a good compatibility of Tf_2O-based tertiary amide activating system with reactive organometallic reagents.[27] Thus, according to Scheme 2, an amide **A**, when treated with Tf_2O and DTBMP,[28c] will generate the highly electrophilic *O*-triflyl imidate **B**, which can react readily with a Grignard reagent to give *N*,*O*-acetal **C**. The latter can eliminate $^-$OTf to generate iminium ion intermediate **D**. The subsequent acidic hydrolysis of **D** will release ketone **1** and amine **6**. Among the three possible intermediates **B**, **C**, and **D**, imidoyl triflate **B** is the most reactive, which lays the foundation of a chemoselective and controlled reaction. Noteworthy is that the keteniminium intermediate **E** could also be generated from the intermediate **B** as demonstrated by the Ghosez [2+2] keteniminium-olefin cycloaddition reaction.[30] Thus milder conditions should be used to avoid its formation.

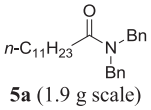
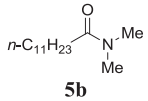
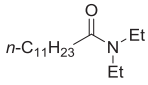
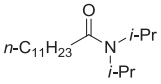
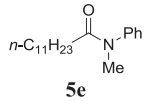
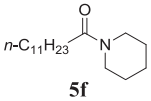
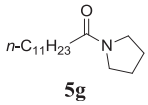
On the basis of these precedents and considerations, we set out to explore the deaminative alkylation of common tertiary amides with Grignard reagents. At the outset of our investigation, the reaction of *n*-butyl Grignard reagent with amide **5a** was selected as a prototype reaction, and the optimal reaction conditions were defined as: treatment of amide **5a** (1.0 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) (1.2 equiv) in dichloromethane with Tf_2O (1.1 equiv) at −78 to 0 °C (2 h), followed by addition of *n*-BuMgBr (1.0 equiv) at −78 °C and stirred for 2 h (−78 to 0 °C). The mixture was warmed up and subjected to acidic hydrolysis to give ketone **1a** in 89% yield (Table 1, entry 1). Notably, the reaction could



Scheme 2. Strategy for the direct transformation of amides into ketones and amines under mild conditions.

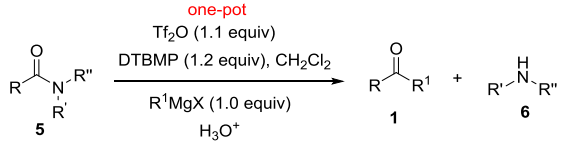
Table 1
Effects of *N*-substituents on the deaminative alkylation of tertiary amides



Entry	Amide	Product (% Yield)[a]
1	 **5a** (1.9 g scale)	**1a** (89) **6a** (86) (R′=R″=Bn)
2	 **5b**	73
3	 **5c**	69
4	 **5d**	53
5	 **5e**	80
6	 **5f**	72
7	 **5g**	70

[a] Isolated yield.

Table 2
Deaminative alkylation of tertiary amides.



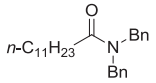
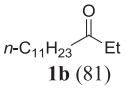
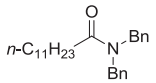
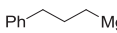
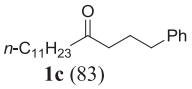
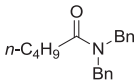
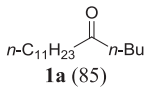
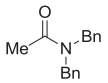
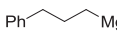
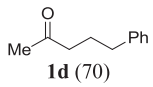
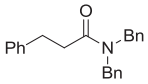
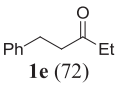
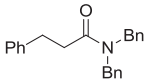
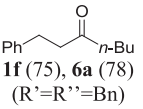
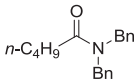
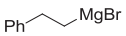
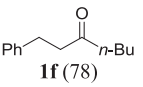
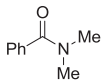
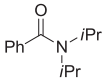
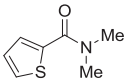
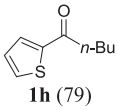
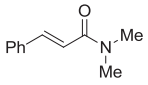
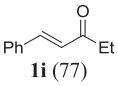
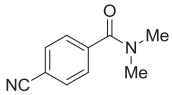
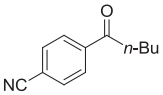
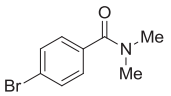
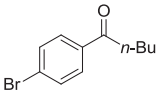
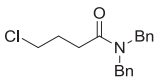
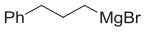
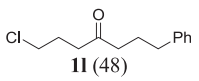
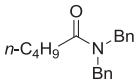
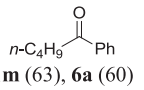
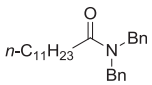
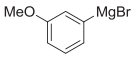
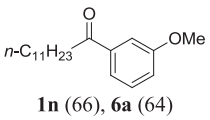
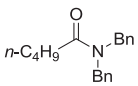
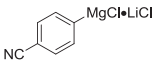
Entry	Amide	RMgX	Product (% yield)[a]
1	 **5a**	EtMgBr	 **1b** (81)
2	 **5a**		 **1c** (83)
3	 **5h**	*n*-$C_{11}H_{23}$MgBr	 **1a** (85)
4	 **5i**		 **1d** (70)
5	 **5j**	EtMgBr	 **1e** (72)
6	 **5j**	*n*-BuMgBr	 **1f** (75), **6a** (78) (R'=R''=Bn)
7	 **5h**		 **1f** (78)
8	 **5k**	EtMgBr	 **1g** (75)
9	 **5l**	EtMgBr	 **1g** (51)
10	 **5m**	*n*-BuMgBr	 **1h** (79)
11	 **5n**	EtMgBr	 **1i** (77)
12	 **5o**	*n*-BuMgBr	 **1j** (67)

Table 2 (*continued*)

Entry	Amide	RMgX	Product (% yield)[a]
13	 **5p**	*n*-BuMgBr	 **1k** (71)
14	 **5q**		 **1l** (48)
15	 **5h**	PhMgBr	 **1m** (63), **6a** (60)
16	 **5a**	 **7**	 **1n** (66), **6a** (64)
17	 **5h**	 **8**	**1j** (65), **6a** (64)
18	**5r**	EtMgBr	**9a** (71)
19	**5s**	EtMgBr	**9b** (79)

[a] Isolated yield.

be performed on gram-scale, and the released dibenzylamine **6a** was isolated in 86% yield through a simple acidic-basic extraction.

After defining the optimal reaction conditions, the effects of *N*-substituents on the reaction were surveyed. As can be seen from Table 1, both acyclic (entries 2–5) and cyclic *N*-alkyl groups (entries 6 and 7) are amenable. While hindered *N*,*N*-diisopropylamide **5d** gave a moderate yield of 53% (entry 4), high yield was obtained with *N*-phenylamide **5e** (entry 5).

The scope of the reaction was further investigated, and the results are displayed in Table 2. A series of reactions on varying acyl moiety and Grignard reagent were examined. As can be seen from entries 1–4, the reaction tolerates alkoyl groups with long (*n*-$C_{11}H_{23}CO$), middle (*n*-C_4H_9CO), and short (CH_3CO) size chains. Phenyl substituted alkanoylamide **5j** reacted similarly to give the corresponding ketones **1e** and **1f** in 72% and 75% yields, respectively (entries 5 and 6). Interestingly, the examples in entries 6 and 7 show that the same ketone can be obtained by a different combination of amides and Grignard reagents. As shown by benzamide **5k** (entry 8), the reaction can be extended to less reactive aroylamides. Even hindered *N*,*N*-diisopropyl benzamide **5l** can be subjected to Grignard reagent addition to give ketone **1g** in 51% yield (entry 9). It is worthy of mentioning that benzamide **5l** is a valuable substrate for both C–H lithiation[14b,k] and C–H functionalization.[15e] However, previously, the transformation of such hindered benzamide derivatives to ketones is challenging except some special cases.[20b] On the other hand, in the tested examples,

different alkyl Grignard reagents ranged from C_2 (entries 1 and 5) to C_{11} (entry 3) reacted smoothly to give the corresponding ketones in similar yields.

We next addressed the issue of chemoselectivity of the reaction. The reductive butylation of thiophenamide **5m**, a heteroaromatic amide, gave **1h** in 79% yield (entry 10). To our delight, as illustrated by cinnamamide **5n** (entry 11), α,β-unsaturated amides reacted chemoselectively at the carbonyl to produce α,β-unsaturated ketones, which are a class of versatile building blocks for organic synthesis and medicinal chemistry.[31] Remarkably, the reaction also tolerated cyano group (entry 12), a functional group with similar reactivity as an amide group. Similarly, the deaminative butylation of *p*-bromobenzamide proceeded efficiently to give bromoketone **1k** in 71% yield (entry 13). Moreover, chloroalkanamide **5q** reacted chemoselectively to yield chloroketone **1l** in 48% yield (entry 14).

Finally, with the aim to expand the method to the synthesis of functionalized aryl ketones and to the deacylation of amides to give amines, we turned our attention to the deaminative arylation. To our delight, following the general procedure, the reaction of **5h** with phenyl magnesium bromide afforded ketone **1m** in 63% yield (entry 15). A simple acidic-basic extraction of the aqueous phase allowed the isolation of dibenzylamine **6a** in 60% yield. This would pave the route for the introduction of functionalized aryl groups. Indeed, treatment of **5a** with Tf_2O and Grignard reagent **7** gave *m*-acylanisole **1n** in 66% yield, along with dibenzylamine **6a** in 64% yield (entry 16). It is worthy of noting that such aryl ketones cannot be synthesized by Friedel–Crafts acylation reaction due to the *o*,*p*-directing property of anisole. More importantly, the deaminative arylation of amide **5h** with functionalized Knochel-Grignard reagent **8**[32] produced smoothly the functionalized ketone **1j** in 65% yield, along with dibenzylamine **6a** in 64% yield (entry 17). Significantly, this approach not only provides a reliable access to aryl ketones that could not be synthesized by Friedel–Crafts acylation reaction, but also opens an avenue to the synthesis of functionalized aryl ketones in view of the ready availability of a large variety of Knochel-Grignard reagents.[32]

In view of the widespread use of acetyl as an amine protecting group, the deacetylation of acetamides **5r** and **5s** were examined. Following the general procedure, the deacetylation proceeded smoothly to give the functionalized piperidines **9a** and **9b** in 71% and 79% yield, respectively (entries 18 and 19).

3. Conclusion

In summary, we have developed a general method for the direct transformation of common tertiary amides into ketones by addition of Grignard reagents. Considering the readily availability of both amides and Grignard reagents, this method is versatile. A number of Grignard reagents can be used in this one-pot reaction. Starting from appropriate functionalized aryl Grignard reagents including Knochel's Grignard reagents, functionalized aryl ketones that cannot be synthesized by the Friedel–Crafts acylation reaction can be synthesized by using this method. Moreover, in addition to employ common amides as convenient and reliable acylating reagents, this method can also be used for the deacylation of amides, widely used protecting forms of amines, to release free amines.

4. Experimental section

4.1. General methods

^1H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 (^1H/400 MHz, ^{13}C/100 MHz) spectrometer. Chemical shifts are expressed in parts per million (δ) relative to an internal standard of residual chloroform (7.26 ppm for ^1H NMR and 77.0 ppm for ^{13}C NMR). Data for ^1H NMR are reported as chemical shift (multiplicity, coupling constant, number of proton). Mass spectra were recorded on a Bruker Dalton ESquire 3000 plus LC-MS apparatus. HRFABMS spectra were recorded on a 7.0T FT-MS. Infrared spectra were recorded with a Nicolet Avatar 330 FTIR spectrometer using film or KBr pellet technique.

Silica gel (300–400 mesh) was used for flash column chromatography, eluting (unless otherwise stated) with ethyl-acetate/petroleum ether (PE) (60–90 °C) mixture. Tf_2O was distilled over phosphorous pentoxide and used within a week. Dichloromethane was distilled over calcium hydride under N_2. All other commercially available compounds were used as received. All reactions were carried out under N_2. All the Grignard reagents were titrated immediately before use.[33]

4.2. General procedure for the direct transformation of tertiary amides into ketones and amines

Tf_2O (1.2 equiv) was added dropwise to a cooled (−78 °C) solution of amide **5** (1.0 equiv) and DTBMP (1.2 equiv) in CH_2Cl_2 (5 mL). The reaction was allowed warming to 0 °C over 2 h. A solution of Grignard reagent (1.0 equiv) in Et_2O was added dropwise to the resultant mixture at −78 °C, and the mixture was stirred at the same temperature for 2 h. The reaction mixture was then quenched with an aqueous solution of 15% HCl (5 mL). The organic layer was separated and the aqueous phase was extracted with diethyl ether (3×5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the desired ketone **1**. To isolate the corresponding amine, the aqueous solution layer was basified with an aqueous solution of 15% NaOH (6 mL), and extracted with dichloromethane (3×10 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the desired amine **6**.

*4.2.1. Hexadecan-5-one (**1a**).* Following the general procedure, the reaction of amide **5a** (380 mg, 1.0 mmol) with *n*-BuMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane=1/50), the known ketone **1a**[10b] (213 mg, yield: 89%) and dibenzylamine **6a**[34g] (168 mg, yield: 86%).

Following the general procedure, the reaction of amide **5b** (227 mg, 1.0 mmol) with *n*-BuMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane=1/50), the known ketone **1a** (175 mg, yield: 73%).

Following the general procedure, the reaction of amide **5c** (255 mg, 1.0 mmol) with *n*-BuMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane=1/50), the known ketone **1a** (156 mg, yield: 65%).

Following the general procedure, the reaction of amide **5d** (283 mg, 1.0 mmol) with *n*-BuMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane=1/50), the known ketone **1a** (127 mg, yield: 53%).

Following the general procedure, the reaction of amide **5e** (289 mg, 1.0 mmol) with *n*-BuMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane=1/50), the known ketone **1a** (192 mg, yield: 80%).

Following the general procedure, the reaction of amide **5f** (267 mg, 1.0 mmol) with *n*-BuMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane=1/50), the known ketone **1a** (173 mg, yield: 72%).

Following the general procedure, the reaction of amide **5g** (253 mg, 1.0 mmol) with *n*-BuMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane=1/50), the known ketone **1a** (158 mg, yield: 66%).

1a: Colorless oil. IR (film) ν_{max}: 2932, 2860, 1716, 1466, 1260, 1129 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J=6.9 Hz, 3H), 0.90 (t, J=7.4 Hz, 3H), 1.22–1.35 (m, 18H), 1.50–1.60 (m, 4H), 2.38 (t, J=7.4 Hz, 2H), 2.39 (t, J=7.4 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 14.1, 22.3, 22.6, 23.9, 26.0, 29.3, 29.3, 29.4, 29.4, 29.6 (2C), 31.9, 42.5, 42.8, 211.6 ppm; MS (ESI) m/z 263 ($M+Na^+$, 100%).

*Dibenzylamine (**6a**).* Pale yellow oil. IR (film) ν_{max}: 3332, 3083, 3061, 3024, 2917, 2817, 1494, 1452, 1109, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.68 (br s, 1H), 3.80 (s, 4H), 7.19–7.40 (m, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.2 (2C), 127.0 (2C), 128.2 (4C), 128.4 (4C), 140.4 (2C) ppm; MS (ESI) m/z 198 ($M+H^+$, 100%).

*4.2.2. Tetradecan-3-one (**1b**).* Following the general procedure, the reaction of amide **5a** (380 mg, 1.0 mmol) with EtMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane=1/50), the known ketone **1b**[34a] (172 mg, yield: 81%). Colorless oil. IR (film) ν_{max}: 2924, 2853, 1716, 1462, 1376, 1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J=6.8 Hz, 3H), 1.05 (t, J=7.3 Hz, 3H), 1.22–1.34 (m, 16H), 1.52–1.62 (m, 2H), 2.39 (t, J=7.3 Hz, 2H), 2.43 (t, J=7.3 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.8, 14.1, 22.7, 23.9, 29.3, 29.3, 29.4, 29.5, 29.6 (2C), 31.9, 35.8, 42.4, 212.0 ppm; MS (ESI) m/z 235 ($M+Na^+$, 100%).

*4.2.3. 1-Phenylpentadecan-4-one (**1c**).* Following the general procedure, the reaction of amide **5a** (380 mg, 1.0 mmol) with (3-phenylpropyl)magnesium bromide gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane=1/50), ketone **1c** (250 mg, yield: 83%). Colorless oil. IR (film) ν_{max}: 3085, 3062, 3027, 2925, 2854, 1715, 1496, 1454, 1370, 746, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J=6.9 Hz, 3H), 1.22–1.33 (m, 16H), 1.49–1.58 (m, 2H), 1.90 (tt, J=7.4, 7.4 Hz, 2H), 2.35 (t, J=7.4 Hz, 2H), 2.40 (t, J=7.4 Hz, 2H), 2.61 (t, J=7.4 Hz, 2H), 7.15–7.32 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 23.8, 25.2, 29.2, 29.3, 29.4, 29.4, 29.6 (2C), 31.9, 35.1, 41.8, 42.9, 125.9, 128.3 (2C), 128.4 (2C), 141.6, 211.1 ppm; MS (ESI) m/z 325 ($M+Na^+$, 100%); HRESIMS calcd for $[C_{21}H_{34}NaO]^+$ ($M+Na^+$): 325.2502; found: 325.2509.

*4.2.4. 5-Phenylpentan-2-one (**1d**).* Following the general procedure, the reaction of amide **5i** (239 mg, 1.0 mmol) with (3-phenylpropyl)magnesium bromide gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane=1/50), the known ketone **1d**[34c] (114 mg, yield: 70%). Colorless oil. IR (film) ν_{max}: 3086, 3062, 3026, 2931, 2860, 1715, 1496, 1453, 1366, 747, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.91 (tt, J=7.5, 7.5 Hz, 2H), 2.11 (s, 3H), 2.43 (t, J=7.5 Hz, 2H), 2.62 (t, J=7.5 Hz, 2H), 7.15–7.31 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2, 29.9, 35.0, 42.8, 125.9, 128.4 (2C), 128.4 (2C), 141.5, 208.7 ppm; MS (ESI) m/z 185 ($M+Na^+$, 100%).

*4.2.5. 1-Phenylpentan-3-one (**1e**).* Following the general procedure, the reaction of amide **5j** (329 mg, 1.0 mmol) with EtMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane=1/50), the known ketone **1e**[34b] (119 mg, yield: 73%). Colorless oil. IR (film) ν_{max}: 3085, 3055, 3027, 2957, 2923, 2851, 1717, 1496, 1455, 1261, 746, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, J=7.4 Hz, 3H), 2.40 (q, J=7.4 Hz, 2H), 2.73 (t, J=7.6 Hz, 2H), 2.90 (t, J=7.6 Hz, 2H), 7.15–7.31 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.7, 29.8, 36.1, 43.9, 126.0, 128.3 (2C), 128.5 (2C), 141.2, 210.6 ppm; MS (ESI) m/z 185 ($M+Na^+$, 100%).

*4.2.6. 1-Phenylheptan-3-one (**1f**).* Following the general procedure, the reaction of amide **5j** (329 mg, 1.0 mmol) with *n*-BuMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane=1/50), the known ketone **1f**[34b] (143 mg, yield: 75%) and dibenzylamine **6a** (153 mg, yield: 78%). Colorless oil. IR (film) ν_{max}: 3085, 3063, 3028, 2958, 2932, 2872, 1714, 1496, 1454, 1370, 748, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J=7.3 Hz, 3H), 1.24–1.34 (m, 2H), 1.49–1.59 (m, 2H), 2.38 (t, J=7.4 Hz, 2H), 2.72 (t, J=7.6 Hz, 2H), 2.89 (t, J=7.6 Hz, 2H), 7.15–7.31 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 22.3, 25.8, 29.7, 42.7, 44.2, 126.0, 128.3 (2C), 128.4 (2C), 141.1, 210.3 ppm; MS (ESI) m/z 213 ($M+Na^+$, 100%).

*4.2.7. Propiophenone (**1g**).* Following the general procedure, the reaction of amide **5k** (149 mg, 1.0 mmol) with EtMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane=1/50), the known ketone **1g** (100 mg, yield: 75%). Colorless oil. IR (film) ν_{max}: 3081, 2921, 2851, 1691, 1261, 746, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, J=7.2 Hz, 3H), 3.00 (q, J=7.2 Hz, 2H), 7.42–7.49 (m, 2H), 7.52–7.58 (m, 1H), 7.94–8.00 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.2, 31.7, 127.9 (2C), 128.5 (2C), 132.8, 136.9, 200.8 ppm; MS (ESI) m/z 157 ($M+Na^+$, 100%).

*4.2.8. 1-(2-Thienyl)-1-pentanone (**1h**).* Following the general procedure, the reaction of amide **5m** (155 mg, 1.0 mmol) with *n*-BuMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane=1/50), the known ketone **1h**[10b] (132 mg, yield: 79%). Colorless oil. IR (film) ν_{max}: 3091, 2958, 2931, 2872, 1661, 1519, 1416, 1264, 722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J=7.4 Hz, 3H), 1.36–1.46 (m, 2H), 1.69–1.78 (m, 2H), 2.89 (t, J=7.4 Hz, 2H), 7.12 (dd, J=5.0, 3.8 Hz, 1H), 7.62 (dd, J=5.0, 1.1 Hz, 1H), 7.71 (dd, J=3.8, 1.1 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 22.4, 26.9, 39.1, 128.0, 131.6, 133.2, 144.5, 193.5 ppm; MS (ESI) m/z 191 ($M+Na^+$, 100%).

*4.2.9. (E)-1-Phenylpent-1-en-3-one (**1i**).* Following the general procedure, the reaction of amide **5n** (175 mg, 1.0 mmol) with EtMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane=1/50), the known ketone **1i**[34d] (123 mg, yield: 77%). Colorless oil. IR (film) ν_{max}: 3081, 3063, 3029, 2926, 2851, 1694, 1671, 1449, 751, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (t, J=7.3 Hz, 3H), 2.70 (q, J=7.3 Hz, 2H), 6.75 (d, J=16.2 Hz, 1H), 7.36–7.42 (m, 3H), 7.51–7.60 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.2, 34.0, 126.1, 128.2 (2C), 128.9 (2C), 130.3, 134.6, 142.2, 200.8 ppm; MS (ESI) m/z 183 ($M+Na^+$, 100%).

*4.2.10. 4-Pentanoylbenzonitrile (**1j**).* Following the general procedure, the reaction of amide **5o** (174 mg, 1.0 mmol) with *n*-BuMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane=1/50), the known ketone **1j**[34e] (125 mg, yield: 67%).

Following the general procedure, the reaction of amide **5h** (281 mg, 1.0 mmol) with Knochel-Grignard reagent **8** gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane=1/50), the known ketone **1j** (121 mg, yield: 65%) and dibenzylamine **6a** (126 mg, yield: 64%).

Colorless oil. IR (film) ν_{max}: 3062, 3037, 2926, 2855, 2233, 1576, 1494, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J=7.3 Hz, 3H), 1.37–1.46 (m, 2H), 1.69–1.77 (m, 2H), 2.98 (t, J=7.3 Hz, 2H), 7.75–7.79 (m, 2H), 8.02–8.06 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 22.3, 26.1, 38.6, 116.2, 117.9, 128.4 (2C), 132.5 (2C), 140.0, 199.0 ppm; MS (ESI) m/z 210 ($M+Na^+$, 100%).

*4.2.11. 1-(4-Bromophenyl)pentan-1-one (**1k**).* Following the general procedure, the reaction of amide **5p** (227 mg, 1.0 mmol) with *n*-BuMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane=1/50), the known ketone **1k**[10b] (170 mg, yield: 71%). Colorless oil. IR (film) ν_{max}: 2958, 2932, 2872, 1687, 1586, 1396, 1204, 1071, 1007, 836, 807 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J=7.3 Hz, 3H), 1.35–1.45 (m, 2H), 1.66–1.75 (m, 2H), 2.93 (t, J=7.3 Hz, 2H), 7.57–7.61 (m, 2H), 7.79–7.84 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.4, 26.3, 38.2, 127.9, 129.5 (2C),

131.8 (2C), 135.7, 199.4 ppm; MS (ESI) m/z 263, 265 ($M+Na^+$, 100%); HRESIMS calcd for $[C_{11}H_{13}BrNaO]^+$ ($M+Na^+$): 263.0042, 265.0027; found: 263.0043, 265.0021.

*4.2.12. 1-Chloro-7-phenylheptan-4-one (**1l**).* Following the general procedure, the reaction of amide **5q** (178 mg, 1.0 mmol) with (3-phenylpropyl)magnesium bromide gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane=1/50), ketone **1l** (108 mg, yield: 48%). Colorless oil. IR (film) ν_{max}: 3084, 3055, 3028, 2962, 2929, 2858, 1713, 1496, 1453, 1265, 739, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.92 (tt, J=7.5, 7.5 Hz, 2H), 2.02 (tt, J=6.6, 6.6 Hz, 2H), 2.43 (t, J=7.5 Hz, 2H), 2.57 (t, J=6.6 Hz, 2H), 2.62 (t, J=7.5 Hz, 2H), 3.56 (t, J=6.6 Hz, 2H), 7.14–7.31 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2, 26.2, 35.0, 39.3, 42.0, 44.5, 126.0, 128.4 (2C), 128.4 (2C), 141.4, 209.5 ppm; MS (ESI) m/z 247 ($M+Na^+$, 100%); HRESIMS calcd for $[C_{13}H_{17}ClNaO]^+$ ($M+Na^+$): 247.0860; found: 247.0863.

*4.2.13. 1-Phenylpentan-1-one (**1m**).* Following the general procedure, the reaction of amide **5h** (281 mg, 1.0 mmol) with PhMgBr gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane=1/50), the known ketone **1m**[10b] (102 mg, yield: 63%) and dibenzylamine **6a** (118 mg, yield: 60%). Colorless oil. IR (film) ν_{max}: 3064, 2959, 1687, 1598, 1449, 1269, 1208, 1118, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J=7.4 Hz, 3H), 1.36–1.46 (m, 2H), 1.67–1.77 (m, 2H), 2.96 (t, J=7.4 Hz, 2H), 7.42–7.48 (m, 2H), 7.51–7.57 (m, 1H), 7.93–7.98 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.4, 26.4, 38.2, 128.0 (2C), 128.5 (2C), 132.8, 137.0, 200.5 ppm; MS (ESI) m/z 185 ($M+Na^+$, 100%).

*4.2.14. 1-(3-Methoxyphenyl)dodecan-1-one (**1n**).* Following the general procedure, the reaction of amide **5a** (380 mg, 1.0 mmol) with 3-methoxyphenylmagnesium bromide **7** gave, after flash column chromatography on silica gel (eluent: EtOAc/*n*-hexane=1/50), the known ketone **1n**[34f] (191 mg, yield: 66%) and dibenzylamine **6a** (126 mg, yield: 64%). Colorless oil. IR (film) ν_{max}: 3074, 3004, 2917, 2850, 1684, 1595, 1460, 1258 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J=6.8 Hz, 3H), 1.22–1.40 (m, 16H), 1.68–1.77 (m, 2H), 2.94 (t, J=7.4 Hz, 2H), 3.85 (s, 3H), 7.07–7.13 (m, 1H), 7.33–7.38 (m, 1H), 7.47–7.50 (m, 1H), 7.51–7.56 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ14.1, 22.7, 24.4, 29.3, 29.3, 29.5, 29.5, 29.6 (2C), 31.9, 38.7, 55.4, 112.3, 119.2, 120.7 (2C), 129.5 (2C), 138.5, 159.8, 200.4 ppm; MS (ESI) m/z 313 ($M+Na^+$, 100%).

*4.2.15. Ethyl piperidine-4-carboxylate (**9a**).* Following the general procedure, the reaction of amide **5r** (199 mg, 1.0 mmol) with EtMgBr gave, after flash column chromatography on silica gel (eluent: MeOH/CH_2Cl_2=1/10), the commercially available amine **9a** (111 mg, yield: 71%). Colorless oil. IR (film) ν_{max}: 3321, 2975, 2940, 2853, 729, 1178, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J=7.1 Hz, 3H), 1.54–1.67 (m, 2H), 1.72 (br s, 1H), 1.84–1.92 (m, 2H), 2.40 (tt, J=11.3, 3.9 Hz, 1H), 2.63 (td, J=12.3, 2.7 Hz, 1H), 3.09 (dt, J=12.7, 3.7 Hz, 2H), 4.13 (q, J=7.1 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 29.2 (2C), 41.6, 45.8 (2C), 60.2, 175.1 ppm; MS (ESI) m/z 158 ($M+H^+$, 100%).

*4.2.16. 4-{[(tert-Butyldiphenylsilyl)oxy]methyl}piperidine (**9b**).* Following the general procedure, the reaction of amide **5s** (395 mg, 1.0 mmol) with EtMgBr gave, after flash column chromatography on silica gel (eluent: MeOH/CH_2Cl_2=1/10), the known amine **9b** (279 mg, yield: 79%). Colorless oil. IR (film) ν_{max}: 3289, 3074, 3049, 2924, 2853, 1470, 1425, 1108, 1069, 823, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.10–1.22 (m, 2H), 1.60–1.76 (m, 3H), 1.93 (br s, 1H), 2.59 (td, J=12.2, 2.4 Hz, 2H), 3.08 (dt, J=11.9, 2.9 Hz, 2H), 3.49 (d, J=6.2 Hz, 2H), 7.34–7.45 (m, 6H), 7.63–7.69 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 26.8 (3C), 30.0 (2C), 39.0, 46.4 (2C), 68.9, 127.6 (4C), 129.5 (2C), 133.9 (2C), 135.6 (4C) ppm; MS (ESI) m/z 354 ($M+H^+$, 100%).

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